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Docket No.: 2846.1001-028

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|---|---|
| Applicants: | David A. Edwards, Giovanni Caponetti, Jeffrey S. Hrkach, Noah Lotan, Justin Hanes, Abdellaziz Ben-Jebria and Robert S. Langer | | |
| Application No.: | 10/090,418 | Group: | 1617 |
| Filed: | March 1, 2002 | Examiner: | Jennifer Kim |
| Confirmation No.: | 8180 | | |

For: **AERODYNAMICALLY LIGHT PARTICLES FOR PULMONARY DRUG DELIVERY**

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

Judy Breen 12/14/04

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Judy Breen

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## SUPPLEMENTAL APPEAL BRIEF

Mail Stop Appeal Briefs Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is being filed pursuant to 37 CFR 1.192. A transmittal letter, fee and request for Oral Hearing were filed on July 29, 2004. The required sections under 37 CFR 1.192 are set forth below under separate headings.

(1) The Real Party of Interest

The real party of interest in this appeal is Massachusetts Institute of Technology and the Penn State Research Foundation by virtue of the Assignment recorded on April 8, 1999 at Reels 9923 and 9925 and frames 0384-0392 and 0098-0102, respectively.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 1-2, 4-11 and 19-21 are pending, finally rejected and appealed. Claims 3 and 12-18 have been canceled.

(4) Status of the Amendments

An "Amendment After Final" which requests reconsideration of the rejections was mailed on May 27, 2004 and received on June 2, 2004. No action has been received in response thereto.

(5) Summary of the Invention

The invention relates to methods of increasing the systemic bioavailability of a hormone, methods of delivering a hormone, and methods of manufacturing particles comprising a hormone. All of the methods are characterized by aerodynamically light particles having an aerodynamic diameter of less than 4.7 microns and a mass mean geometric diameter of at least 5 microns. The particles have excellent delivery efficiency via inhalation to the pulmonary system. The hormone that is administered thereby is highly bioavailable systemically with an excellent duration of therapeutic benefit, as evidenced by prolonged and detectable serum levels.

(6) Issues

The issues on appeal are:

(1) whether the Office has established that the claims are prima facie obvious over Platz et al. (US Patent 6,423,344);

(2) whether the Terminal Disclaimers filed on December 18, 2003 overcome the obviousness-type double patenting rejections over the previous patents granted to the Applicants in the parent applications of this application.

(7) Grouping of Claims

Claims 5-9, 15, 16, and 19-21 do not stand or fall with Claims 1, 2, 4, 10, and 11.

(8) Argument

(a) **35 USC § 103**

The Examiner has rejected Claims 1, 2, 4-11 and 19-21 under 35 USC § 103 (a) as being unpatentable over Platz et al. (USPN 6,423,344 B1). The Examiner states that Platz teaches methods of delivering therapeutic agents such as insulin or testosterone along with pharmaceutical carriers and excipients to the lung of a patient particles having a mass mean diameter of less than 10 microns and particles having a diameter of 0.4- 5 microns. While the Examiner admits that the reference (1) does not teach the release profile of an insulin product as recited in the claims; (2) does not teach particles having a size of at least 20 microns recited in Claim 6; and (3) does not teach the tap density recited in Claims 19-21, the Examiner asserts, without any support, that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase the mass mean diameter of the particles. It would have been obvious to recite the instant release profiles in the claims.
>
> One of ordinary skill in the art would have been motivated to increase the mass mean diameter of the particles because employment of larger particles in a pulmonary inhalation method is known in the art. Note the same composition,

administered in the same manner would be reasonably expected to exhibit the same release profile.
With regard to the specified tap density set forth in claims 19-21 would be a property of the particle employed in the prior composition comprising very same particle with very same size. Therefore the prior art composition would possess same tap density as claimed by the very same particle employed by the Applicants.

(b) **The Rebuttal**

The Examiner appears to first assume that the product of the invention is the same as that of Platz. Because of this first and fundamental assumption, she assumes that all of the properties and distinguishing characteristics are inherent. Of course, such an analysis is factually incorrect and legally and procedurally inappropriate. She provides absolutely no technical reasoning or basis for her conclusions and assumptions. For this reason alone, the rejection should be reversed. Furthermore, please note that many patents have already been granted to very similar subject matter. This Examiner's position is completely contrary to the positions taken by numerous patent examiners before her. Nonetheless, the following statements are made.

Is Platz Prior Art?

Platz is a US Patent that issued from a patent application filed on February 4, 2000, well after the claimed priority date of the present invention. While it claims priority as a continuation or continuation-in-part to various prior applications, some of which have a filing date prior to the claimed priority dates, the Examiner has made no effort to actually establish that any of these prior applications contain the disclosures relied upon in the rejection. The Examiner has failed to satisfy her burden in this proceeding.

Geometric Size of Platz's Particles

Platz teaches compositions for therapeutic administration, one route of which is by inhalation. The vast majority of the teachings ***require*** the particles to be less than 5 microns in size. Obviously, if the particles are less than 5 microns in size, then the mass mean diameter of these particles is less than 5 microns in size and the particles are

outside the scope of the present claims. At Column 2, line 9, it states that "The particles being delivered are usually less than 5 μm in size..." Platz states, at Column 2, lines 44-51:

> For pulmonary delivery, it is ***critical*** that the average particle size be maintained below 5 μm, preferably in the range from 0.4 μm to 5 μm, and that the amount of the composition comprising particles outside of the target size range be minimized. (emphasis added.)

Platz states at Column 4, lines 12-16:

> It has been found that control of the concentration of the total solids below 5% significantly enhances the ability to obtain dried particles in the desired size range, i.e., below 5 μm, and preferably in the range from 0.4 μm to 5 μm.

Platz states at Column 7, lines 63 et seq.:

> In particular, the dry particles ***will*** have an average particle size below 5 μm, more preferably being in the range from 0.4-5 μm, preferably from 0.4-4 μm, and most preferably from 0.4-3 μm. The average particle size of the powder will be measured as mass mean diameter (MMD) by conventional techniques.

Further, each and every composition in Table 2 has a particle size less than 5 microns. Thus, in numerous places, Platz teaches that the small size is "*critical*" or essential.

With respect to the range of sizes within the particles, Platz states, at Column 2, lines 44-51:

> Preferably, at least 90% by weight of the powder will have a particle size in the range from 0.1 μm to 7 μm. More preferably, at least 95% will have a size in the range from 0.4 μm to 5 μm. (emphasis added.)

Platz states at Column 5, lines 27-34:

> It has been found that proper control of the atomization and drying conditions can produce a dried powder having at least 90% of the mass of particles in the size range from 0.1 μm to 7 μm, more preferably having at least 95% in the size range from 0.4 μm to 5 μm, thus permitting the output of the drying step to be collected and the powder used without the need to size classify the product prior to packaging.

Again, Platz states at Column 6, lines 14-17,

> Preferably, 90% by weight of the compositions will comprise particles having a particle size in the range from 0.1 μm to 7 μm, more preferably 95% in the range from 0.4 μm to 5 μm.

Platz states at Column 8, lines 14-21:

> Usually, the ultrafine dry powders ***will*** have a size distribution where at least 90% of the powder by weight ***will*** comprise particles having an average size in the range from 0.1 μm to 7 μm, with preferably at least 95% being in the range from 0.4 μm to 5 μm. Additionally, it is desirable that the particle size distribution avoid having an excess amount of particles with very small average diameters, i.e., below 0.4 μm.

Platz teaches that it is ***critical*** for pulmonary delivery for the particles to be less than 5 microns in size. While some of these citations permit particles to be present in the composition with a size greater than 5 microns, the mass mean diameters of these compositions are not disclosed. Thus, where a powder has at least 90% of the powder in the 1-7 micron range, it doesn't necessarily follow that the mass mean diameter will be greater than 5 microns, thereby satisfying the claim limitation. In fact, it would be very difficult to achieve a particle composition which has a 90% of the powder with a size of less than 7 microns and a mean of greater than 5 microns.

Please consider what a bell curve for such a particle population could look like. If 90% of the particles are between 0.1 microns and 7 microns, then the mass mean diameters of these "targeted" populations would certainly be expected to be less than 5 microns. Indeed, if at least 90% of the particles are between 0.1 and 10 microns, with a size distribution of 2, the mass mean geometric diameter of the particles will be less than

5 microns. In no event does this teaching *suggest* a mass mean diameter of greater than 5 microns. Indeed, given the teachings of criticality, one would *select* a mass mean diameter of less than 5 microns, not greater than 5 microns.

It is acknowledged that there are two sentences which appear to be inconsistent with the above so-called "critical" or essential teachings. At Column 6, lines 4-9, it is stated that the "compositions comprise particles having an average particle size below 10 μm..." At Column 8, lines 25-27, it is taught that a particle size distribution having a mean between 3 and 10 microns will deliver to the central airways.

However, even if one were to ignore the ***critical*** and essential teachings set forth elsewhere in the document and grant these contradictory teachings full value for its scope, this is not the only claim limitation that must be met by Platz to render the claimed invention obvious, as will be discussed below.

Further, with respect to Claims 5, 6, 15 and 16, Platz nowhere suggests that the administration of particles *greater* than 10 or 20 microns can be used. There is absolutely no support in this record that such particles were known for pulmonary delivery, contrary to the assertion by this examiner. Indeed, this position is completely contrary to the findings made by the numerous other examiners who have prosecuted the related applications to this application.

Site of Delivery of Platz's Particles

Platz does not teach that it is desirable and obvious to deliver a drug, such as a hormone (e.g., insulin or testosterone), for systemic delivery by administering a composition comprising large particles (e.g., having a mass mean diameter of greater than 5 microns) and a low aerodynamic diameter (less than 4.7 microns), as claimed.

The claims require that the aerodynamic diameter be less than 4.7 microns. Nowhere does Platz teach the desired aerodynamic diameters of the particles. In Table 2, the mass median aerodynamic diameter for one run is disclosed as being 3.3 microns. This one run discloses an MMAD which is greater than the geometric diameter. That is, Platz makes very small particles (i.e., less than 5 microns) because he desires to deliver to

the alveoli. Larger particles (i.e., greater than 5 microns) are taught to deliver to the central and upper airways. See Column 8, lines 25-27.

The present inventors were the first to discover that improved compositions can be achieved by delivering large particles which behave like very small particles. Indeed, Applicants have been awarded a number of patents in this regard. For all the reasons the prior examiners have granted these earlier patents, these claims are likewise not obvious over the teachings of Platz. Platz does not teach the combination of larger particles with lower aerodynamic diameters to achieve systemic delivery.

Indeed, the teaching in Column 8 with respect to products in the 3 to 10 micron range suggests that such particles would be expected to deliver to the central airways. One would not administer to the central airways to achieve systemic delivery but rather would deliver to the deep lung or alveoli. Thus, this is a clear teaching away from the present invention which administers a hormone systemically using large particles.

Duration of release

Most of the claims recite the duration of release achieved. Claims 1-6, 10 and 11 require that the drug releases for at least 4 hours. The Examiner infers, without support, that this is an inherent property of the particles of Platz. Of course, this is clearly not true. Duration of release requires, among other things, good and efficient delivery and high bioavailability. Indeed, a particle population that delivers the drug poorly to the lung will not meet the claim limitation. Platz provides no data on delivery to show systemic bioavailability for any of its products. Platz suggests that large products will deliver to the upper and central airways, which the Examiner has certainly not shown would be expected to result in good systemic bioavailability.

Attached please find another patent (US Patent 6,737,045) by the same group of investigators that show that even their preferred and very small insulin products do not have the long duration of release claimed in the present claims. Thus, it is clearly not an inherent result of any and all particles that may theoretically be made according to the procedures of Platz.

The assertion made by the Examiner in the rejection above is, "Note the same composition, administered in the same manner would be reasonably expected to exhibit the same release profile." The rejection assumes that the Platz composition is the same as that claimed. The Examiner has not shown that the claimed composition is the same as Platz's compositions. They are not. Platz teaches, generically and specifically, only small particles. The claims are directed to large particles. Further, not even all small particles have the same release profile. Thus, the statement is factually incorrect and does not support the burden of proof required to maintain a rejection.

The Examiner states, "It would have been obvious to recite the instant release profiles in the claims." The sentence is not understood. The issue is not whether it is obvious, given the success achieved by the Applicant, to draft the claim and include the novel limitations achieved by the Applicant within the claim. Indeed, such an analysis would be a classic and impermissible hindsight reconstruction. Or is the Examiner trying to say that the release profile claimed is obvious? If so, then the above statements should suffice to show the error in the conclusion.

With respect to Claims 7-9, these claims do not stand or fall with the remaining claims. Claim 7 requires release for at least 10 hours. Claim 8 requires release for at least 24 hours and Claim 9 requires release for at least 48 hours. Platz does not teach the claimed duration of release.

The Tap Density of Platz's Particles

Again, the Examiner asserts without any support, that the Platz particles have a tap density that falls within the scope of the claims. Of course, this is untrue. The mathematical relationship between geometric diameter, density and aerodynamic diameter are set forth on page 11 of the present specification. Where the geometric diameter is essentially the same as the aerodynamic diameter, the density is about 1 $g/cm^3$. Where the geometric diameter is greater than the aerodynamic diameter, the density is greater than 1 $g/cm^3$. Where the geometric diameter is less than the aerodynamic diameter, the density is less than 1 $g/cm^3$.

Turning to the examples of Platz, it becomes clear that not one of the powders described have a size in the claimed range. Each example possesses a geometric diameter of less than 3 microns. The density is simply not disclosed. A desired or preferred density is not disclosed. Even if one were to calculate the theoretical density utilizing the formula of Patentee's specification, it becomes clear that particles possessing low density were not desired. These calculations are provided below in the Table, which readily illustrates that the combination of large geometric diameters, low density and low aerodynamic diameters is not described or taught by Platz.

TABLE

| Platz Example | MMD (microns) (%<5 microns) | MMAD (microns) (%<5 microns) | Density ($g/cm^3$) (calculated) |
|---|---|---|---|
| 1 | 1.3-1.5 | 2.0 (90%) | 2.4-1.8 |
| 2 | 2.4-2.7 | ND | NA |
| 3 | 1.95 (100%) | 3.2 (77%) | 2.7 |
| 4 | 2.74 (97%) | 4.1 (64%) | 2.2 |
| 5 | 1.3 | ND | NA |
| 6 | 1.71 | 1.0 (90%) | 0.34 |
| 7 | 1.62 (95%) | 2.0 (85%) | 1.5 |
| 8 | 2.06 (89%) | 2.5 (84%) | 1.5 |
| 9 | ND | 3.5 (70%) | NA |
| 10 | 2.5 | 3.2 (70%) | 1.6 |
| 11 | 2 | 2.4 (75%) | 1.4 |
| 12 | 2.3 | 1.8 (80%) | 0.61 |

ND indicates that the parameter was not disclosed. NA indicates insufficient information to complete calculation.

Clearly, Platz does not teach or suggest the unique combination of particle characteristics, generically or specifically, claimed herein. Tap density is not inherent to

each and every product that can be made according to the teachings therein. In contrast to the assertion made by the Examiner, products of the same size do not necessarily have the same tap density. The Examiner is factually incorrect in her assertions. Products of the same size and composition can have different densities. Thus, the products of Platz do not inherently anticipate or even render obvious this limitation. Therefore, Claims 19-21, which specifically recite a tap density, are separately patentable.

The Claimed Combination

The claims are directed to the combination of large porous particles that have a small aerodynamic diameter which contain a hormone, such as insulin or testosterone, and have at least 4 hours release upon systemic delivery. Platz not only teaches that a low geometric diameter is "critical" and essential for inhalation, the only teaching of a larger particle is in the context of local, non-systemic delivery. There is no evidence that suggest that such products are suitable for systemic delivery of a hormone such as insulin. There is no basis for assuming that such products would be capable of achieving such a long duration of release. The claims are directed to specific selection invention which the Examiner completely dismisses as being a combination of inherent features. She only gets there by assuming, without any basis, that the claimed products are identical to those of Platz. Indeed, this is a backwards analysis and is legally impermissible.

(c) **Double Patenting**

The Examiner has rejected the claims under the judicially created doctrine of obviousness-type double patenting over various patents which share common inventorship, common priority and are directed, generally, to the same subject matter.

(d) **Rebuttal**

Applicants have filed two terminal disclaimers (one signed by each assignee of the present application), without prejudice, to render these rejections moot. The Office has not yet acknowledged receipt or entry of these terminal disclaimers. Copies are again

enclosed herewith as well as a copy of the postcard receipt. The rejection should be withdrawn or reversed.

(9) The Conclusion

Having established that the Examiner has failed to establish a prima facie case of obviousness and the unexpected results achieved by the present invention, Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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By _____
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Chelmsford, MA 01863
Dated: 12/13/04

**Pending Claims**

1. (Original) A method of increasing systemic bioavailability of a hormone administered by inhalation comprising:

administering to the respiratory system of a patient or animal in need of said hormone aerodynamically light particles that have a mass mean diameter greater than 5 μm, an aerodynamic diameter less than 4.7 μm and that include said hormone,

wherein the particles are delivered and deposited to the patient's or animal's lungs and the hormone is released in the patient's or animal's blood stream for at least 4 hours.

2. (Original) The method of Claim 1 wherein the hormone is insulin.

3. (Canceled)

4. (Original) The method of Claim 1 wherein the particles further include a biodegradable material.

5. (Original) The method of Claim 1 wherein the mass mean diameter is greater than 10 μm.

6. (Original) The method of Claim 1 wherein the mass mean diameter is greater than 20 μm.

7. (Original) The method of Claim 1 wherein the hormone is released in the patient's or animal's blood stream for at least 10 hours.

8. (Original) The method of Claim 1 wherein the hormone is released in the patient's or animal's blood stream for at least 24 hours.

9. (Original) The method of Claim 1 wherein the hormone is released in the patient's or animal's blood stream for at least 48 hours.

10. (Original) A method of delivering a hormone to the pulmonary system to a patient or animal, comprising:

administering, via inhalation, particles that include a hormone and a biodegradable material, have an aerodynamic diameter less than about 4.7 μm and a mass mean diameter greater than about 5 μm,

wherein the hormone is delivered and deposited in the patient's or animal's lungs and is released in the patient's or animal's blood stream for at least 4 hours.

11. (Amended) A method of increasing the bioavailability of a hormone, comprising:

administering to a patient or animal, via inhalation, particles that include a hormone and a biodegradable material, have an aerodynamic diameter less than about 4.7 μm and a mass mean diameter greater than about 5 μm,

wherein the hormone is delivered and deposited in the patient's or animal's lungs and is released in the patient's or animal's blood stream for at least 4 hours.

12-18. (Canceled)

19. (New) The particles of Claim 1, further comprising a tap density less than about 0.4 $g/cm^3$.

20. (New) The particles of Claim 10, further comprising a tap density less than about 0.4 $g/cm^3$.

21. (New) The particles of Claim 11, further comprising a tap density less than about 0.4 $g/cm^3$.

# TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

In re Application of: David A. Edwards, Giovanni Caponetti, Jeffrey S. Hrkach, Noah Lotan, Justin Hanes, Abdellaziz Ben-Jebria and Robert S. Langer

Application No.: 10/090,418

Filed: March 1, 2002

Confirmation No.: 8180

For: AERODYNAMICALLY LIGHT PARTICLES FOR PULMONARY DRUG DELIVERY

The owner, Massachusetts Institute of Technology and The Penn State Research Foundation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent Nos. 5,874,064; 5,855,913; 6,436,443; 5,985,309; 6,503,480; and 6,254,854. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The terminal disclaimer fee under 37 CFR 1.20(d) is enclosed.

The undersigned is empowered to act on behalf of the owner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date _____

_____
Signature

_____
Typed or printed name

_____
Massachusetts Institute of Technology

Date 11/4/03

Ronald J. Huss
Signature

Ronald J. Huss
Typed or printed name

Director Intellectual Property Office

The Penn State Research Foundation

# STATEMENT UNDER 37 C.F.R. § 3.73(b)

The Penn State Research Foundation (Name of Assignee), a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.),

states that it is

A. [ X ] the assignee, together with Massachusetts Institute of Technology, of the entire right, title and interest in the patent application(s)/patents identified in the attached Attachment A; or

B. [ ] an assignee together with [ ] of the entire right, title and interest in the patent application identified above.

The right, title and interest of the above-named assignee in the patent application identified above is established by virtue of:

A. [ X ] An assignment from the inventor(s) of the patent application(s)/patents identified in Attachment A. The assignment was recorded in the Patent and Trademark Office at the Reel(s) and Frame(s) indicated in Attachment A, or a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s) of the patent application identified above, to the current assignee as shown below:

1. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame ____, or a copy thereof is attached.

2. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame ____, or a copy thereof is attached.

3. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame ____, or a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Date: June 6, 2003

Name: Ronald J. Huss

Title: Director, Intellectual Property Office

Signature: Ronald J. Huss

# TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

In re Application of: David A. Edwards, Giovanni Caponetti, Jeffrey S. Hrkach, Noah Lotan, Justin Hanes, Abdellaziz Ben-Jebria and Robert S. Langer

Application No.: 10/090,418

Filed: March 1, 2002

Confirmation No.: 8180

For: AERODYNAMICALLY LIGHT PARTICLES FOR PULMONARY DRUG DELIVERY

The owner, Massachusetts Institute of Technology and The Penn State Research Foundation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent Nos. 5,874,064; 5,855,913; 6,436,443; 5,985,309; 6,503,480; and 6,254,854. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The terminal disclaimer fee under 37 CFR 1.20(d) is enclosed.

The undersigned is empowered to act on behalf of the owner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 12/8/03

Signature

Rita H. Filipowicz

Typed or printed name

Massachusetts Institute of Technology

Date _____

Signature

Typed or printed name

The Penn State Research Foundation

# STATEMENT UNDER 37 C.F.R. § 3.73(b)

Massachusetts Institute of Technology (Name of Assignee), a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is

A. [X] the assignee, together with The Penn State Research Foundation, of the entire right, title and interest in the patent application(s)/patents identified in the attached Attachment A; or

B. [ ] an assignee together with [ ] of the entire right, title and interest in the patent application identified above.

The right, title and interest of the above-named assignee in the patent application identified above is established by virtue of:

A. [X] An assignment from the inventor(s) of the patent application(s)/patents identified in Attachment A. The assignment was recorded in the Patent and Trademark Office at the Reel(s) and Frame(s) indicated in Attachment A, or a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s) of the patent application identified above, to the current assignee as shown below:

1. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame _____, or a copy thereof is attached.

2. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame _____, or a copy thereof is attached

3. From: To:
The document was recorded in the Patent and Trademark Office at
Reel , Frame _____, or a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Date: May 23, 2003

Name: Rita M. Filipowicz

Title: Patent Administrator

Signature: Rita M. Filipowicz